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REVIEW

Neurobiology of social behavior abnormalities in autism and Williams syndrome

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Social behavior is a basic behavior mediated by multiple brain regions and neural circuits, and is crucial for the survival and development of animals and humans. Two neuropsychiatric disorders that have prominent social behavior abnormalities are autism spectrum disorders (ASD), which is characterized mainly by hyposociability, and Williams syndrome (WS), whose subjects exhibit hypersociability. Here we review the unique properties of social behavior in ASD and WS, and discuss the major theories in social behavior in the context of these disorders. We conclude with a discussion of the research questions needing further exploration to enhance our understanding of social behavior abnormalities.

Introduction to social behavior

One of the most complicated behaviors humans and animals can perform is social behavior, which takes place between conspecifics and results in social relationships. Social behavior is based on the ability to properly communicate with others; individuals must sense, process and interpret social cues, as well as respond with appropriate behaviors. These functions are mediated by brain areas comprising the "social brain"[1], in particular, the medial prefrontal cortex (mPFC), amygdala, anterior insula, anterior cingulate cortex, inferior frontal gyrus and superior temporal sulcus (**Fig. 1**).

Two neuropsychiatric developmental disorders, ASD and WS, result in contrasting abnormalities in social behavior[2]: while ASD is characterized by social avoidance and lack of interest in social interactions, WS is characterized by uninhibited social interactions and overfriendliness. Although the opposing social behavior phenotypes of ASD and WS offer an opportunity to study neurobiological mechanisms of social abnormalities, the heterogeneity of ASD symptoms and genetics makes it complicated to directly compare the contrasted social behaviors. By contrast, the well-characterized genetic information of WS and its distinctive behavioral phenotype make the study of its neurogenetics more accessible and could help to understand the relationship among genes, neural circuitry, physiology and social behavior. In this review, we compare and contrast the symptoms, genetics and related clinical findings of these two disorders with the hope that further comparative studies will uncover underlying neurobiological mechanisms of social behavior abnormality.

Contrasting social behavior abnormalities in ASD and WS

Autism spectrum disorders. ASDs are a group of heterogeneous neurodevelopmental disorders characterized according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by (i) deficits in social communication and social interaction and (ii) stereotyped, repetitive behavior[3] with narrow restricted interests[4], often accompanied by sensory abnormalities and language development delay or absence. These symptoms must be present in early childhood and impede the individual's everyday activity. Autism, from the Greek words *autos* ("self") and *ismos* ("action"), was described initially by Kanner in 1943 (ref. 5) as a congenital lack of interest in other people. Nowadays, ASD affects 1 in 68 children in the United States[6] (but see ref. 7), with approximately five times as many boys affected as girls[8].

ASD is one of the most heritable common psychiatric disorders, indicating that genetics are central to ASD etiology. Nevertheless, the genetic contribution to pathophysiology is challenging to explore because of incomplete penetrance, a large number of susceptibility genes, and complex gene–environment interactions. While genome-wide association studies have yet to yield replicable common variants for ASD, possibly owing to small sample sizes, studies of copy number variants and single nucleotide polymorphisms have provided gene candidates for further study[9–14]. Many of the ASD-linked genes encode synaptic proteins[15] at glutamatergic synapses (**Fig. 2** and **Supplementary Table 1**), most of them acting postsynaptically[16], indicating that excitatory synaptic dysfunction may be a key pathophysiology in ASD. However, our understanding of the molecular architecture of inhibitory synapses is very limited, so further studies on the basic biology of inhibitory synapses may shed new lights on etiology and pathology of ASD.

Deficient social behavior in ASDs. Although ASDs are heterogeneous in etiology and symptoms, a common central feature is social behavior deficit unrelated to cognitive dysfunction[4]. Part of the deficit includes impairments in social interaction, such as the inability to initiate social interactions or develop relationships, lack of social or emotional reciprocity, lack of interest in others' emotions[17], communication deficits including impaired speech development and poor expressive language[18], impairment in nonverbal social interaction, and lack of interest in sharing enjoyment and interests with others[19].

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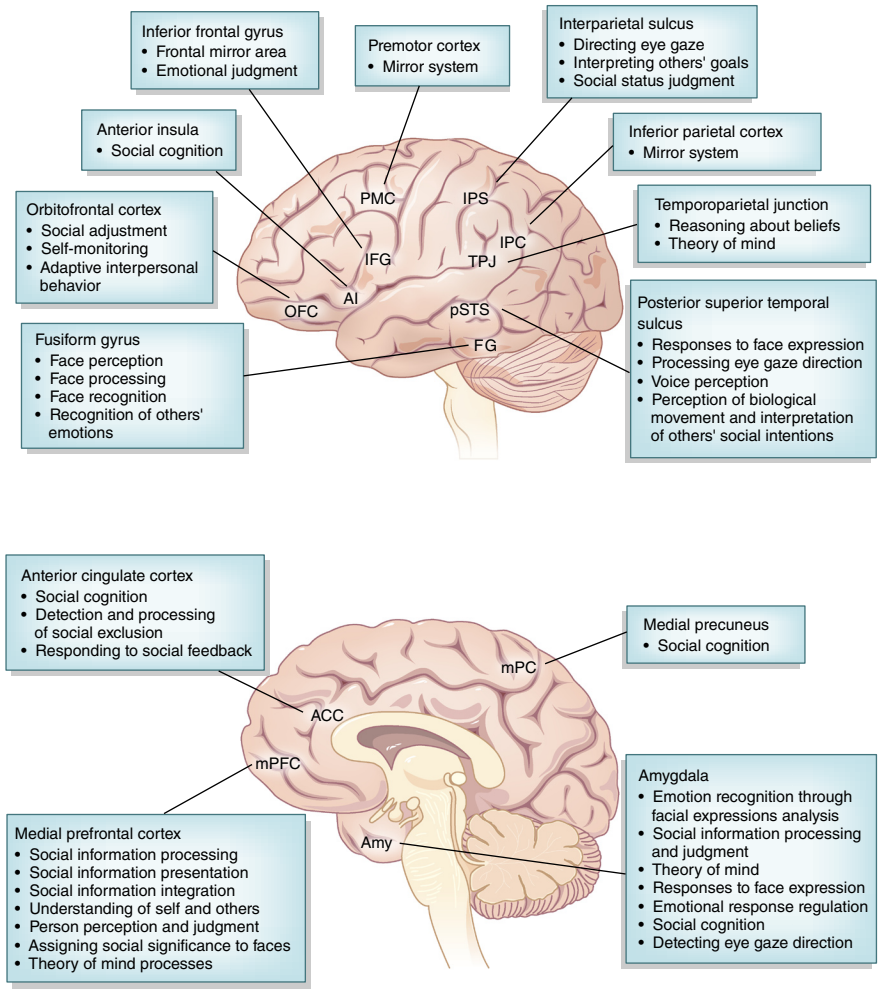

Figure 1 Anatomical and functional brain areas related to social behavior. Brain regions of high relevancy to social behavior, participating in the different aspects of social behavior and their contribution to social behavior.

The earliest evidence of impaired social behavior that arises during the course of ASD is impaired selective attention and lack of innate preference of newborns for human voice[20] and face[21] over other sounds and visual stimuli. Infants with ASD demonstrate impaired joint attention[22], the ability to share eye gaze focus on an object following the alert of one individual to the other by pointing or gazing. In typical older children, the increased ability to communicate verbally with others results in more complex social behavior, including shared play and interactions with other children; these abilities, impaired in children with ASD[23], emphasize the profound differences between a typical child and one with ASD and are one of the major alerts for testing the child for ASD. These social behavior deficits continue in adults with ASDs, impairing their behavior.

Williams syndrome. WS or Williams-Beuren syndrome is a rare multisystemic neurodevelopmental genetic disorder named after John C.P. Williams, who was the first to describe the syndrome in 1961 (ref. 24). Physically, WS is associated with cardiovascular difficulties, growth abnormalities, connective tissue and endocrine abnormalities, and specific 'elfin' facial and physical anomalies. Mentally, WS is associated with distinctive central cognitive and personality profiles, independent of IQ, which include overfriendliness (frequently termed the "cocktail party personality"), increased empathy, mental retardation[25], strength in verbal and language skills[26], weaknesses in visual-spatial skills[27], increased musical interest and emotional reactivity to music[28] and elevated anxiety derived from fear and specific phobias[29].

WS prevalence is between 1 in 7,500 (ref. 30) and 1 in 20,000 (ref. 31) individuals, and is caused by a hemizygous deletion of about 25 genes at the 7q11.23 region on chromosome 7 (ref. 32). These genes are part of the WS chromosome region (WSCR), estimated to be about 1.6 megabases, the typical deletion in ~95% of subjects. The other ~5% of subjects have longer deletions of ~1.84 megabases[33,34] or other extremely rare types of deletions[35–37].

Interestingly, individuals with one or two extra copies of the WSCR genes due to WSCR duplication (Dup7) have an ASD-related phenotype characterized by developmental impairments, poor eye contact, anxiety disorder, repetitive behavior, hyposocial behavior and severe expressive language delay, which is the most commonly reported feature of Dup7 (refs. 38–42), although the range of these phenotypes is larger and much less studied than in WS. Overall, these phenotypes suggest that WSCR genes are dosage-dependent and may affect language skills and development.

Hypersociability in WS. Although WS is characterized by multiple physiological and mental features, the hypersociability phenotype is a striking feature of WS and seemingly the opposite of the typical phenotype seen in ASDs. This unique social behavior is the reason why, in one of the first studies to characterize subjects with WS, they were described as individuals who "love everyone, are loved by everyone, and are very charming"[43].

In WS, the gregarious personality is characterized by a consistent increased interest in and approach to strangers[44], overfriendliness that is positively correlated with age[45,46], and excessive empathy but poor social judgment ability. One of the main reasons suggested for the hypersociability in WS is the substantial attention bias toward any kind of social stimuli, with a special interest in human faces[47] (but see ref. 48), in contrast to the behavior seen in subjects with ASDs.

The distinctive intense gazing pattern begins at infancy and continues throughout development[49]. While processing faces, individuals with WS demonstrate atypical patterns, with increased focus on faces and eyes[47] that lasts longer than in typically developed controls[50].

Toddlers and young children with WS continue showing higher sociability behavior, as measured by parental ratings of their child's social behavior[51], and by their high engagement in dyadic, face-to-face interactions compared to control children[52]. Hypersociability persists in older children[45] and into adulthood, in which a longitudinal study found improved yet still abnormal social and adaptive functioning[53].

Another difficulty for subjects with WS is accurate perception of emotions. In particular, individuals with WS demonstrate difficulties in detecting social fear signals given through facial expressions and voices[54] and show less arousal in response to angry faces[55] than

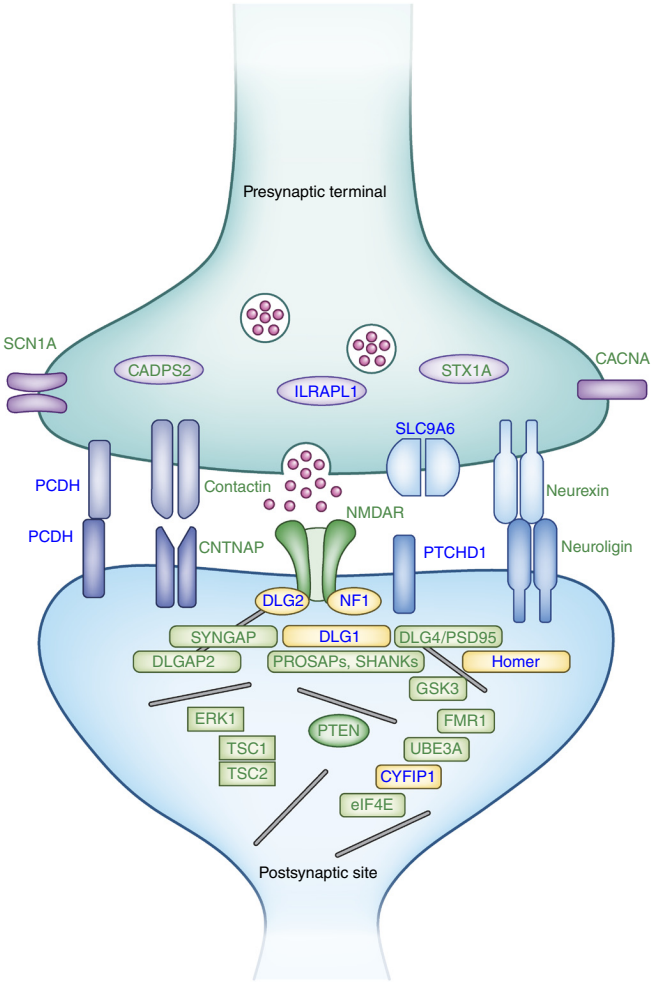

Figure 2 Synaptic proteins at the glutamatergic synapse encoded by ASD-related genes. These synaptic proteins participate in the formation, stabilization and function of the synapse. Proteins in which a mutation in their encoding genes affects social behavior are marked in green, while those with no direct evidence are marked in blue. Presynaptic proteins are SCN1A (sodium channel protein type 1), CADPS2 (calcium-dependent secretion activator 2), ILRAPL1 (interleukin-1 receptor accessory protein-like 1), STX1A (syntaxin-1A), CACNA (voltage-dependent calcium channel subunit-α), PCDH (protocadherin), contactin, SLC9A6 (sodium-hydrogen exchanger) and neurexin; postsynaptic proteins are PCDH, CNTNAP (contactin-associated protein), NMDAR (glutamate receptor), PTCHD1 (patched domain-containing protein 1), neuroligin, DLG2 (Disks large homolog 2), NF1 (neurofibromin 1), PROSAPs (SH3 domain and ankyrin repeat containing proteins) and SHANKs (proline-rich synapse-associated proteins), homer, GSK3 (glycogen synthase kinase-3), ERK1 (mitogen-activated protein kinase 3), TSC1 (tuberous sclerosis 1), TSC2 (tuberous sclerosis 2), PTEN (phosphatase and tensin homolog), FMR1 (fragile X mental retardation protein), UBE3A (ubiquitin protein ligase E3A), CYFIP1 (cytoplasmic FMR1-interacting protein-1), and eIF4E (eukaryotic translation initiation factor 4E).

non-impaired controls. Individuals with WS also tend to have greater attention bias for positive than negative facial expression[56], and they rate happy faces[57] and unfamiliar faces[58] as more approachable than do control subjects.

A key factor that affects the cognitive phenotype in individuals with WS is the location of the shorter atypical microdeletions. Studies have found a classic behavioral and neurodevelopmental phenotype in cases where the atypical deletion includes the usual telomeric breakpoint, which results in deletion of the genes general transcription factor 2I (*Gtf2i*)[59] and *Gtf2i* repeat domain containing 1 (*Gtf2ird1*) from the general transcription factor 2I gene family[60,61]. But, in cases where *Gtf2i* and *Gtf2ird1* genes are not deleted, only a mild behavioral and neurodevelopmental phenotype was found[37,62,63], suggesting that *Gtf2i* and *Gtf2ird1* deletion is important in the etiology of the behavioral and neurodevelopmental phenotype of WS.

Gtf2i encodes transcription factor II-I (TFII-I), a highly conserved and ubiquitously expressed multifunctional transcription factor that contains DNA-binding-I repeat domains, a leucine zipper and a nuclear localization signal[64]. TFII-I regulates gene expression through interactions with tissue-specific transcription factors and complexes related to chromatin remodeling[65]. Most WSCR deletions include both genes because *Gtf2i* and *Gtf2ird1* genes are in close proximity to each other; however, *Gtf2i* deletion has been shown to be more important for the WS social behavior phenotype. For example, by comparing the social behavior phenotype in rare cases of microdeletions sparing *Gtf2i* to those with the full WSCR deletion, Dai *et al.*[66] found the behavioral phenotype of the patient with the spared *Gtf2i* to be less social. Similarly, in individuals with different microdeletions sparing *Gtf2i*, Morris *et al.*[62] found a WS cognitive profile but no mental retardation or intellectual difficulties. *Gtf2i* was also suggested to be highly involved in other neurobehavioral impairments of subjects with WS[35]. In contrast, a patient with haploinsufficiency for *Gtf2ird1* but normal *Gtf2i* expression levels demonstrated normal social behavior but a delay in language acquisition[67].

In mice, homozygous deletion of *Gtf2i* causes embryonic lethality and severe developmental impairments[68], including neural tube defects and exencephaly. Heterozygous deletion of *Gtf2i* in mice results in impaired social habituation to an unfamiliar mouse, leading to increased time spent investigating the unfamiliar mouse as compared to that in wild-type mice[69]. In a three-chamber social interaction and recognition test, *Gtf2i* heterozygous mice demonstrated about 50% higher preference ratio for interacting with an unfamiliar mouse than a novel object, compared to wild-type mice[69].

It is not known how transcriptional dysregulation resulting from *Gtf2i* deletion can lead to the hypersocial phenotype in WS, and there is no clear overlap in transcriptional dysregulations between WS and ASD. A recent study using induced pluripotent stem cells found that in the pluripotent state *Gtf2i* is already responsible for 10–20% of the transcriptional dysregulation in disease-relevant pathways in WS and Dup7 (ref. 70). It is therefore possible that transcriptional dysregulation as a result of *Gtf2i* deletion could result in impaired development of neural circuits that are crucial for normal social behavior from the very earliest development stages.

Etiology of social behavior abnormalities

Although the etiology of social behavior abnormalities in ASD and WS is still unclear, researchers have identified many associated anatomical and physiological changes. Because of the limitations inherent in studying human subjects, basic molecular and cellular research in animal models is crucial to better understand mechanisms underlying social behavior. Indeed, findings from animal studies have led to the development of several theories that relate to social behavior. However, humans and animals have evolved under different evolutionary pressures. Because of this evolutional divergence, while molecular and cellular functions are largely comparable, social behaviors are much harder to compare. This is due to differences between animals and humans in the complexity of social behaviors, as well as the underlying motivations. Moreover, the sensory cues that lead to social response in these two groups

are substantially different and hence rely on the proper function of different neural circuits.

We will focus on three key theories, representing the physiological, functional, and systemic aspects of the theories in the field of social behavior. Since social behavior has been highly studied in the frame of ASD, these theories relate mainly to ASD rather than WS.

Social cognition in human studies. To properly perform social behavior, an individual needs to acquire, process, store and use social input from the environment to decide on and take proper social actions, the sum of which is called social cognition. Social cognition also relates to the process of understanding others or one's own thoughts, mental states and feelings ("theory of mind," or mentalization)[71]. This process is impaired in children with ASD[72] and may result in impaired social information analysis and abnormal responses[73]. These functions involve mainly the functionality of cortical brain regions (**Fig. 1**). Hence, cortical dysfunction might lead to cognitive dysfunction in general, and specifically to impairments in social cognition and sensory integration. Importantly, it is still unknown why social cognition is specifically impaired in subjects with otherwise normal cognition.

Cortical dysfunction can be the result of improper development of the cortex; in early stages of development, genes determine and regulate the formation of the brain, including its cells, synapses and neural circuits. However, later the complex interaction between genes and the subject's environment may lead to alterations in brain development that will result in an inability to respond to the environment[74]. Genetic mutations can lead, for example, to improper synapse formation or imbalanced cellular activity between GABAergic and glutamatergic neurons. This may result in lack of proper development and function of inhibitory circuits that are essential for balanced neural activity during critical periods, and similar development and functional issues in brain regions and circuits essential for social behavior[75]. A lack of early experience-dependent development may result in impaired development of primary sensory circuits, for example, which could lead to further impairments in more complex functions, governed by higher-order neural circuits that develop later. Consequently, the social brain does not receive proper stimulation and experience with integrating and processing social-related inputs, nor with the execution of social decisions and actions, leading to social disabilities.

Following this logic, and focusing for example on the need to properly process social information, improper function of cortical and subcortical brain regions results in sensory integration and multisensory processing problems, and indeed, sensory abnormalities are found in 90% of children with ASD[76]. Not properly integrating and processing the social information around them, overstimulated subjects may have difficulties in changing their attention to social-related information, resulting in improper social orientation that causes behavioral deficits. Overwhelmed by stimuli, subjects with ASD might therefore tend to perform repetitive movements that return them to their 'safe zone' and relieve their anxiety.

Because most ASD and WS research focuses on subjects of toddler age and older, prenatal and early postnatal processes responsible for early development deficits are less understood (for review, see ref. 77). Consequently, it is difficult to differentiate between causes and effects: that is, whether a primary disruption of brain development leads to social abnormalities or whether an improper interaction with the environment leads to undeveloped social-related brain regions. Thus, more research needs to be done during infancy and followed up in a longitudinal manner, as this will also enable earlier diagnosis, earlier intervention, and identification of earlier-acting mechanisms. This can be addressed by studying infants at high familial risk for ASD as part of prospective longitudinal studies[78].

A recent longitudinal magnetic resonance imaging (MRI) study examined the morphology of the corpus callosum in infants at high risk for ASD, as compared to low-risk controls. The findings from this study showed significantly increased corpus callosum area and thickness in children who were later diagnosed with ASD spectrum disorder starting at 6 months of age[79]. An additional longitudinal MRI study on the development of white matter pathways in infants at high-risk for ASD found higher fractional anisotropy in 6-month-old subjects with ASD, followed by blunted developmental trajectories, resulting in lower fractional anisotropy by 24 months (ref. 80). Another study suggested that an increased cortical surface area, resulting from an increased rate of brain growth before age 2, is responsible for the brain enlargement in children with ASD[81]. More specifically, this enlargement in ASD toddlers is attributed to a generalized cerebral cortical enlargement, with an excessive temporal lobe white matter enlargement[81]. Yet another longitudinal MRI study also found cerebral enlargement in ASD toddlers, including both gray and white matter, with the highest degree of enlargement in frontal, temporal and cingulate cortices[82]. Interestingly, a different study on 6-month-old infants at high risk and their low-risk controls did not find significant differences in intracranial, cerebrum, cerebellum or lateral ventricle volume or head circumference[83]. Additionally, young boys with ASD had decreased volumes of white matter and the dorsolateral region of the frontal cortex as compared with control subjects, suggesting delayed development of these regions[84].

Imaging studies in adult ASD patients support changes particularly in mPFC. An MRI study found that subjects with ASD have decreased mPFC activation during mentalizing and weaker functional connectivity of the mPFC to other brain regions, as compared to control subjects[85]. These findings suggest that subjects with ASD use different neural circuits and patterns of activation than control subjects to analyze their own and other people's emotions. Another study demonstrated that the mPFC is also involved in joint attention in subjects with ASD[86]: it found a lack of signal differentiation and atypical pattern of dorsal mPFC activation in subjects with ASD compared to control subjects during a task that required joint attention. Lastly, studies have demonstrated abnormal local connectivity[87,88] as well as abnormal long-range connectivity in ASD subjects, with the latter linked to altered development of white matter in multiple brain regions (for review, see ref. 89). However, the cellular mechanisms underlying these axonal disorganizations are not fully known.

In support of the imaging findings, histological examination of the frontal cortices of subjects with ASD has found abnormal neuronal morphology[90] and reduced minicolumns[91], suggesting that improper development of this cortical area might play a role in impaired social input integration.

Frontal lobe dysfunction is also related to the WS hypersociability profile, as those regions have a role in regulating and suppressing actions that are socially inappropriate. The relatively low intelligence of patients with WS presents a challenge when comparing cortical function between subjects with WS and their control groups; it is important to select experimental and control subjects with comparable levels of intelligence. Examining subjects with WS who had normal intelligence, Meyer-Lindenberg *et al.* showed abnormal activity of the prefrontal cortex, including the orbitofrontal cortex (OFC), as a function of task, as compared to normal controls[92]. Additionally, Meyer-Lindenberg *et al.* found relatively reduced task-based connectivity between OFC and the amygdala in subjects with WS compared to controls[92]. Functionally, lesions of the OFC were associated with

social disinhibition, suggesting that abnormal OFC activity in subjects with WS might be responsible for the disinhibition of social approach. Deficits in regulating actions were suggested to be responsible for the high social approach behaviors of subjects with WS, resulting in poor social response inhibition due to frontal lobe dysfunction[93,94]. Indeed, Porter *et al.* showed similarities in social approach suppression in subjects with WS and those with frontal lobe damage[94]. Both types of subjects express impulsive social approach behavior and verbalize inappropriate thoughts, likely as a result of poor response inhibition[94]. This was also noted in a recent study in children with WS, which demonstrated that frontal lobe–controlled response inhibition capability is the strongest indicator of social approach behavior[95]. Lastly, abnormal cortical activity in subjects with WS was observed in the right OFC, showing an opposite pattern of OFC activation in response to positive and negative emotional faces[96]. Moreover, this same study showed reduced activation of the right amygdala in response to negative faces as compared to that in typically developing controls[96].

Cortical dysfunction revealed by animal studies. Although the neurophysiological substrates for social behavior abnormalities are unknown, on the basis of human and animal model studies we may speculate that excitatory-inhibitory (E/I) neuronal activity imbalance might explain the physiological mechanism of social behavior abnormalities[97]. Changes in the E/I balance can result in hyper-[98] or hypoactivation[99] of specific brain regions and lead to dysfunction of the affected brain regions. For example, elevated excitatory activity specifically in mouse mPFC results in impaired social behavior[100], and, consistent with the E/I imbalance theory, elevated activation of inhibitory cells rescues the social deficits[100].

On a genetic level, the association of genes with social behavior is not straightforward, despite multiple animal models showing synaptic or circuit dysfunction accompanied by social behavior abnormalities. For instance, E/I imbalance can occur in cortical regions as a result of mutations in synaptic proteins such as Shanks[98,101], a family of key postsynaptic density (PSD) proteins located in glutamatergic synapses that, together with other postsynaptic proteins (SAPAP and PSD-95), forms a postsynaptic scaffolding complex (**Fig. 2**)[102–104]. While ASD is considered a polygenic disorder in most cases, recent studies showed that genetic disruption of *Shank2* and *Shank3* in mice results in substantial physiological and biochemical alterations at synapses that may contribute to impaired social behavior[99,105–110].

The importance of E/I balance in the cortex was also demonstrated in a mouse model of Rett syndrome[111]. Methyl-CpG-binding protein 2 (MeCP2) regulates the expression of many genes by acting as a transcriptional activator and repressor, and mutations in *Mecp2* are known as the primary cause of Rett syndrome. Specific deletion of *Mecp2* from either all GABAergic neurons in the nervous system (using *Viaat-Cre* mice) or a specific subset of GABAergic neurons in the forebrain (using *Dlx5/6-Cre* mice) resulted in mice with features of Rett syndrome and ASD (**Supplementary Table 1**)[112]. Deletion of *Mecp2* resulted in a reduced inhibitory quantal size, demonstrating that specific disruption of inhibitory signaling is sufficient to recapitulate ASD behaviors[112].

Social cognition relies on proper sensing and integration of sensory and social input, and indeed, sensory abnormalities are common in ASD. Recently, two studies on mouse models of ASD demonstrated the importance of the inhibitory system in sensory input processing and integration. Impaired maturation of the inhibitory system in the insula cortex of BTBR mice results in decreased inhibitory neurotransmission and increased excitatory neurotransmission, affecting multisensory integration[98]. Treatment with a benzodiazepine, a positive modulator of GABAergic transmission, rescues the impairment when provided early in postnatal development, but not when provided at a later age[98]. Furthermore, the GABA-B agonist (*R*)-baclofen has also been shown to reverse social deficits in BTBR mice[113]. In another study, impaired function of the inhibitory system affected sensory input processing in the somatosensory barrel cortex of juvenile mice with an R451C substitution in Nlgn3 (neurologin 3)[114], a postsynaptic protein important for trans-synaptic cell adhesion (**Fig. 2**). Cellot *et al.* recently showed that R451C mutation affects the probability of GABA release from parvalbumin-expressing interneurons, impairing their modulation of principal cells in layer IV of the somatosensory barrel cortex[114]. This leads to a shift in E/I balance and affects the generation of cortical gamma rhythms associated with high cognitive functions such as social behavior.

Currently, neurobiological knowledge of the role of synaptic signaling in WS is extremely limited. Therefore, it would be of great interest to study the developmental abnormalities at the molecular and cellular levels that lead to cortical dysfunction in WS.

The amygdala theory. The amygdala, an almond-shaped region comprising at least 13 nuclei with unique functions, is part of the limbic system. The amygdala, which is highly connected to brain regions responsible for sensory input and autonomic systems, takes part in central functions and processes that are crucial for proper social behavior and emotional processing, and hence is suggested as a central component of the social brain (**Fig. 1**). The amygdala's roles in social behavior include the processing of emotional reactions, memories and visual social stimuli; creation and control of anxiety; and recognizing social emotion from faces. The amygdala also has a central role in the recognition of faces and facial emotion, and in mediating eye gaze[115], such that subjects with complete amygdala lesions, like those with ASD, show impaired eye contact[116]. In high-functioning subjects with ASD, an impaired ability is found in recognizing social information from faces, as in subjects with focal bilateral amygdala damage[117]. Additionally, impaired social judgment was demonstrated in subjects with amygdala lesions[118]; conversely, deep-brain stimulation of the amygdala improved social behavior in a boy with ASD[119].

Anatomically, children with ASD have larger right and left amygdala volumes than those without, although this difference is gone by adolescence[120]. An increased amygdala volume was found also in subjects with WS[121,122], together with a positive correlation between right amygdala volume and the approachability of faces[122]. These findings support the notion that abnormalities in amygdala development and function may contribute to deficits in social judgment, emotional information processing and face expression perception, leading to abnormal emotional reactions and social behavior abnormalities in ASD and WS. Current knowledge is still contradictory, and the opposing social behaviors seen in ASD and WS offer a research approach to link the function of the amygdala and its effects on social behavior.

Abnormal amygdala activity in response to faces has been found in both ASD and WS imaging studies. Hyperactivation of the amygdala was demonstrated when subjects with ASD, as compared to controls, looked at faces[123]. Furthermore, those with ASD gazed more away than toward the eyes of a presented face, as compared to controls, with a greater amygdala response in subjects with ASD while fixating on the eyes rather than the mouth[124]. This suggests that, in ASD, the amygdala response to faces has a negatively valenced overarousal response. However, other studies showed hypoactivation of the amygdala of subjects with ASD while interpreting emotional states by viewing human eyes[125] or while processing human fearful faces[126]. In subjects with WS, amygdala reactivity to fearful faces,

presented as negative social stimuli, was drastically attenuated compared with controls[127], and, strikingly, subjects with WS showed no amygdala activation in a face-discrimination task[128]. The attenuated amygdala activity in WS may result in deficient processing of social-related information, leading subjects to rate strangers' faces as highly approachable[58]. In contrast, higher amygdala reactivity was observed in participants with WS in response to happy faces presented as positive social stimuli[127].

The common hyperactivation of the amygdala in the two disorders, but in response to opposite stimuli, demonstrates the complexity of amygdala functionality and its relevance to social behavior. Subjects with ASD display aversion-related amygdala activation while eye gazing, resulting in eye contact avoidance. In contrast, the appetitive-related amygdala activation observed in subjects with WS may serve to functionally increase attention to and processing of happy faces. It might be that different subpopulations of neurons, such as glutamatergic or GABAergic, are active in response to the stimuli in these disorders, resulting in the contrasting behavioral phenotypes. Indeed, a recent study showed that in the medial amygdala, a brain region modulating innate social behavior, inhibitory neurons are important in controlling social behavior, while excitatory neurons modulate repetitive asocial behavior[129].

When presented with non-social scenes[130], or threatening scenes but not threatening faces[92], subjects with WS show increased amygdala activation and abnormal activation of prefrontal regions linked to the amygdala as compared to controls. Indeed, the amygdala–prefrontal circuitry has been shown to be important in the proper representation of the emotional salience of a stimulus (for review, see ref. 131). Normally, the amygdala's output activity is attenuated by the regulation of mPFC excitatory neurons that project and regulate inhibitory neurons in the basolateral amygdala (BLA) or by intercalated cells around the BLA that inhibit output from the central nucleus of the amygdala[132]. Impairments in this circuitry lead to impaired detection of danger, resulting in lower levels of fear and hypersocial behavior, as demonstrated in human and animal models[133,134]. OFC–amygdala connectivity was functionally disconnected and impaired in subjects with WS[92], suggesting that impaired prefrontal-regulated inhibition of the amygdala is responsible for the dissociated fear in those subjects, who demonstrate high non-social fear along with low social-related fear. A recent study identified the deficits in the structural integrity of prefrontal–amygdala white matter pathways as the primary cause of this pathology[135]. These findings suggest that increased amygdala activation may play a role in non-social scenarios and the increased generalized anxiety and phobias associated with WS.

The overfriendliness in individuals with WS coexists with non-social anxiety and phobias, suggesting they have lower levels of anxiety that are specific to social stimuli. Indeed, WS and social anxiety disorder (SAD) have multiple opposing characteristics, including general social drive, specific approach to unfamiliar people, social behavior in an unfamiliar social environment, and attention to faces and eye gaze (for review, see ref. 136). Functionally, in subjects with WS, hypoactivation of limbic regions is detected during facial emotion processing when compared to control subjects, while subjects with SAD demonstrate hyperactivation, in addition to hyperactivation in medial frontal regions[136]. This suggests that neural circuits that govern general fear are more functionally separated than those related to social fear and that the latter are oppositely affected in SAD and WS.

Lastly, the amygdala also regulates anxiety, making a simple interpretation of the discussed findings difficult. A direct correlation between anxiety levels and social impairment was observed in the case of ASD[137], as well as WS[138]. However, in the case of WS, subjects demonstrate hypersociability along with high anxiety levels. While MRI studies find similar abnormalities in the amygdala in both disorders, the social behavioral phenotypes are opposite, suggesting that subcircuits in either the amygdala or other brain regions upstream or downstream from the amygdala play a role in the opposite social behavior phenotype.

Overall, future studies are needed to better determine the amygdala's valence and function in social behavior, to define the interplay between impaired social behavior and anxiety, and to study whether the different amygdala functions rely on different nuclei that might be oppositely affected in ASD and WS. Since imaging and manipulating the different nuclei of the amygdala is technically difficult in humans, animal models for ASD and WS are valuable research tools for dissecting these questions.

The social motivation theory. The "social motivation theory" suggests that impaired motivation to engage in reciprocal social interaction leads to the ASD-like social deficit[139]. Three key brain regions are related to social motivation and are all highly connected neuroanatomically: orbital and ventromedial regions of the prefrontal cortex, the amygdala, and the ventral striatum. Supporting this theory, children with ASD have a reduced frontostriatal response to socially but not monetarily rewarded learning[140]. However, other studies found the deficit in reward processing in subjects with ASD to be attributable not only to social reward, but also to a more general deficit of the reward system[141]. It is therefore important to determine whether in ASD the impairment is specifically in social motivation or in general motivation, and to study the interplay between the two.

Perhaps one of the most studied molecular mechanisms related to the modulation of social behavior is oxytocin, a neuropeptide synthesized in the hypothalamus, released by the pituitary and affecting the CNS[142]. Oxytocin is involved in increasing the degree of approach behavior, social recognition, social memory, the recognition of others' emotions, emotional information processing, maternal behavior and in reducing social fear and anxiety.

Recent studies tested whether oxytocin signaling in mice plays a part in the reward aspect of social interaction[143]. Oxytocin was found to be an enforcement signal in social behavior, acting in medium spiny neurons of the nucleus accumbens (NAc), where it modifies excitatory synaptic transmission by evoking presynaptic long-term depression[143]. Through its abolition in mice, oxytocin was demonstrated to be necessary for social memory, and oxytocin-null mice demonstrate social amnesia that is rescued upon exogenous oxytocin administration[144].

Additional recent studies in mice support the role of reward circuitry in social behavior and show that the ventral tegmental area (VTA), a major source of dopamine in the reward circuitry, is highly active during social interaction[145]. Bidirectional control of dopaminergic cells in the VTA modulates social behavior in opposite directions[145]. Additionally, activation of the VTA–NAc projection increases social interaction, while VTA–mPFC activation does not affect social interaction, and postsynaptic NAc dopamine receptor D1 medium spiny neurons were shown to be responsible for social behavior regulation[145]. Finally, a study on social attachment in monogamous voles showed that dopamine transmission, specifically in the rostral shell of the NAc, promotes pair-bond formation, with D1-like receptor activation decreasing and D2-like receptor activation increasing pair-bond formation[146].

Future directions

Recent development of genome editing techniques such as TALEN[147] and CRISPR[148] will allow us to develop better animal models of

disease, such as primates[149], for social behavioral studies. In particular, the common marmoset, a small New World monkey with rapid reproduction cycles, could contribute to the next generation of genetically engineered models for brain disorder research[150]. Common marmosets are small (~350 g), reach sexual maturity at 12—16 months, give birth twice a year, and produce 2—3 offspring with each birth. Marmosets are evolutionarily much closer to humans than rodents in brain structure and function; furthermore, marmosets are very social and communicative and can perform some higher cognitive tasks developed for macaque monkeys. Because of the complexity of genetics in ASD, it would be beneficial to start with monogenic causes of ASD, such as *Shank3* and *Chd8* (chromodomain helicase DNA binding protein 8). For WS, *Gtf2i* would be an excellent candidate for genetic manipulation in marmosets on the basis of knowledge gained from both human and mouse studies. Together, these enabling technologies and new models will likely push the field forward significantly in the next few years.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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